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Novel entry into oxepane–diquinane and oxepane–sterpurane hybrids: synthesis and photochemistry of 3-oxatricyclo[7.2.2.$0^{1,7}$]tridecenones

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This paper is dedicated to Professor Paul Knochel, scholar and teacher

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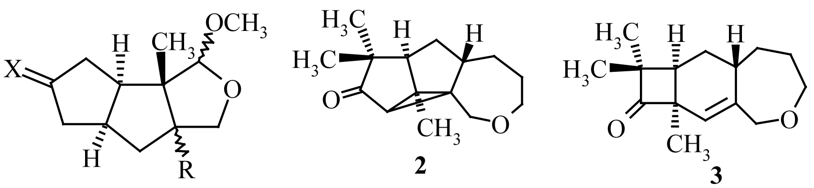
Abstract—A new synthesis of 3-oxatricyclo[7.2.2.$0^{1,7}$]tridecenones via intramolecular $\pi^{4s}+\pi^{2s}$ cycloaddition in cyclohexa-2,4-dienones is described. Their photochemical reactions leading to oxepane–diquinane and oxepane–sterpurane hybrids are depicted. The crystal structure of a key intermediate is also presented. © 2002 Elsevier Science Ltd. All rights reserved.

There is considerable interest in the diquinanes fused with oxygen heterocycles **1** and congeners. They have shown promising biological activity and have proven to be useful for the treatment of leukemia, osteosarcoma, breast and ovarian cancer.[1,2] In view of this and the growing interest in design and synthesis of new molecules which combine structural features of different classes of compounds,[3,4] we considered developing a synthetic route to compounds **2** and **3** (Fig. 1) in which an oxepane ring is fused to a diquinane and a bicyclo[4.2.0]octane ring, respectively. The oxepane ring was chosen since it is present in many natural products that display interesting biological profiles.[5,6] Compound **3** possesses structural features of sterpuranes, another class of biologically active sesquiterpenes.[7] We anticipated that compounds of type **2** and **3** would result from the *endo* tricyclic compound **4** in a stereoselective fashion via photochemical 1,2- and 1,3-acyl shifts, respectively (Scheme 1). It was expected that the desired tricyclic compound **4** could be prepared from the aromatic precursor **7** via **5** and **6** (Scheme 1).

The aromatic precursor **7** was readily prepared from **8** by *O*-alkylation with 5-bromo-1-pentene using NaH in THF and subsequent acid hydrolysis of the acetonide moiety (Scheme 2).[8] Compound **7** was oxidized with



2

3

1a, R = α- H, X= CH_2, O
b, R = β - H, X= CH_2,O

Figure 1.

Keywords: intramolecular cycloaddition; photoreactions; oxa-di-π-methane rearrangement.

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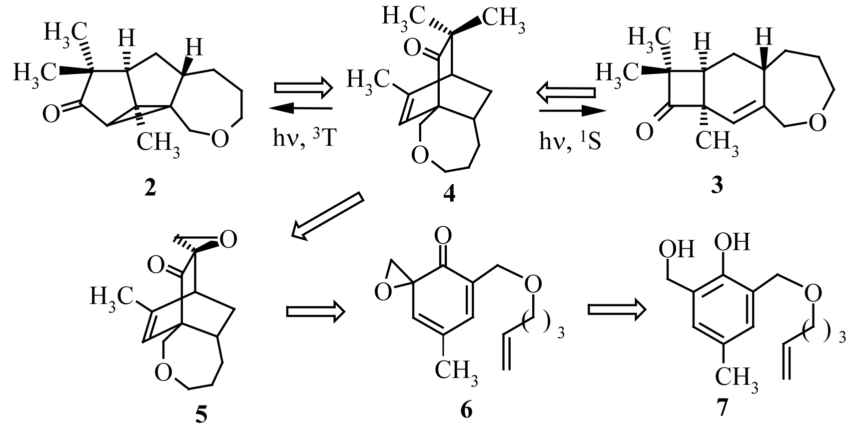
sodium metaperiodate following a procedure of Adler which was modified and further developed in our laboratory.[9] However it did not give the desired ketoepoxide **5**. Instead, the dimer **9** was obtained as a result of intermolecular cycloaddition. Therefore, **9** was converted to the bis-chlorohydrin **10** by treatment with dil. HCl in dioxane which on heating at 160°C in *o*-dichlorobenzene gave **12** in 68% (Scheme 2).

Alternative structures **12a** and **12b** could not be ruled out unequivocally on the basis of 600 MHz NMR spectroscopy, but X-ray crystallographic analysis firmly established structure **12** and the stereochemistry of the cycloaddition (Fig. 2).[10] The *endo* adduct **12** was formed as a result of a retro Diels–Alder reaction of **10** to the monomer **11** followed by intramolecular cycloaddition.

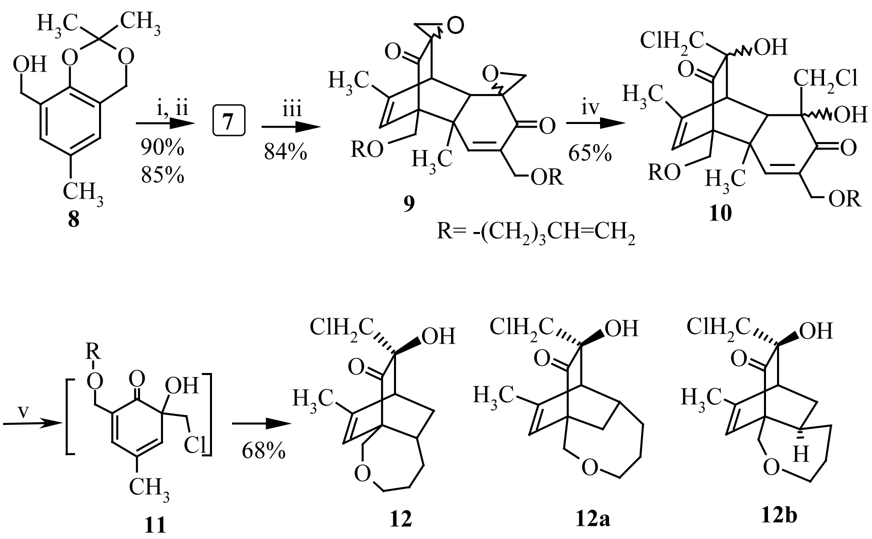
Treatment of **12** under basic conditions gave the keto-epoxide **5** in 92%. Reduction of keto-epoxide **5** with zinc in dioxane containing ammonium chloride gave the compounds **13** and **14** in a ratio of 3:1 (63% yield). Alkylation of **13** with MeI in the presence of NaH–THF gave **4**, while oxidation of **14** followed by decarboxylation furnished the ketone **15** (Scheme 3).

Having developed a route to the tricyclic systems **4**, **5** and **15**, the photochemical reactions of **4** and **5** were investigated. A solution of **4** in acetone (both as a sensitizer and solvent) was irradiated for 1 h to give compound **2** in 64% yield as a result of a 1,2-acyl shift.[11–13] Irradiation of **4** in benzene for 20 min gave the linearly fused tricyclic compound **3** (40%), along with unreacted starting material. Compound **3** is a product of a 1,3-acyl shift.[12,13]

Next we explored the photochemical behavior of **5** since it contains an α-keto-oxirane functional group as well as a constrained β,γ-enone system. No appreciable photochemical reaction of the keto-epoxide **5** was observed in acetone (solvent and sensitizer) over a period of 3 h. Therefore, a solution of **5** in acetone containing acetophenone as a sensitizer was irradiated which gave in addition to the starting material, compound **16** in 15% yield as a result of oxa-di-π-methane rearrangement (Scheme 4).



Scheme 1.



Scheme 2. *Reagents and conditions*: (i) NaH, 5-bromo-1-pentene, THF, Δ; (ii) $HClO_4$, acetone–H_2O; (iii) $NaIO_4$, aq. CH_3CN; (iv) HCl, dioxane; (v) *o*-dichlorobenzene, sealed tube, 160°C.

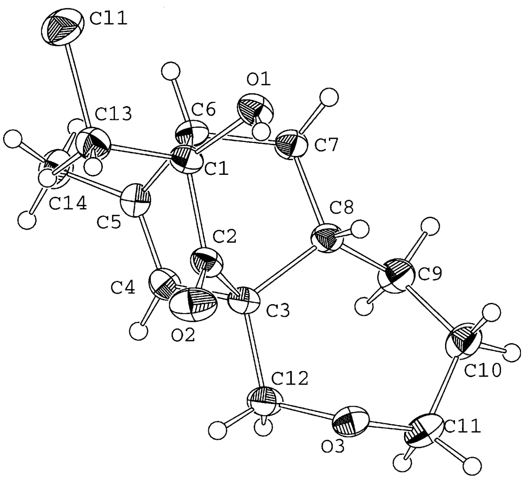


Figure 2. ORTEP diagram of compound **12**.

In summary, a new method for the synthesis of 3-oxatricyclo[7.2.2.0^{1,7}]tridecanes having a β,γ-enone chromophore via intramolecular $\pi^{4s}+\pi^{2s}$ cycloaddition in cyclohexa-2,4-dienone is presented. A stereoselective entry into compounds of type **2** and **3** from a common precursor **5** is described. Interestingly, triplet excitation of the keto-epoxide **5** gave the product **16** as a result of oxa-di-π-methane rearrangement.

Acknowledgements

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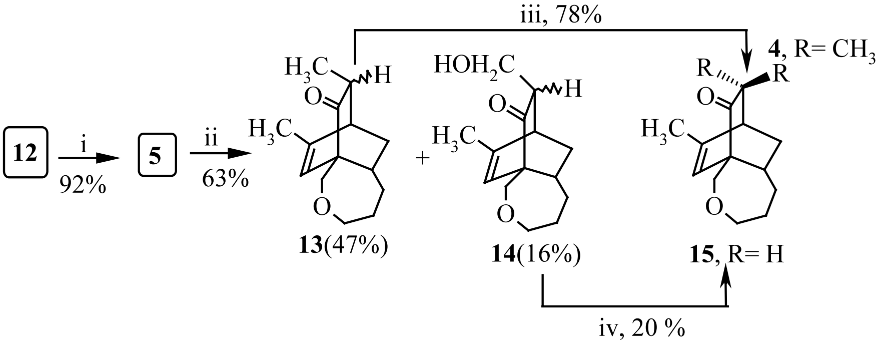
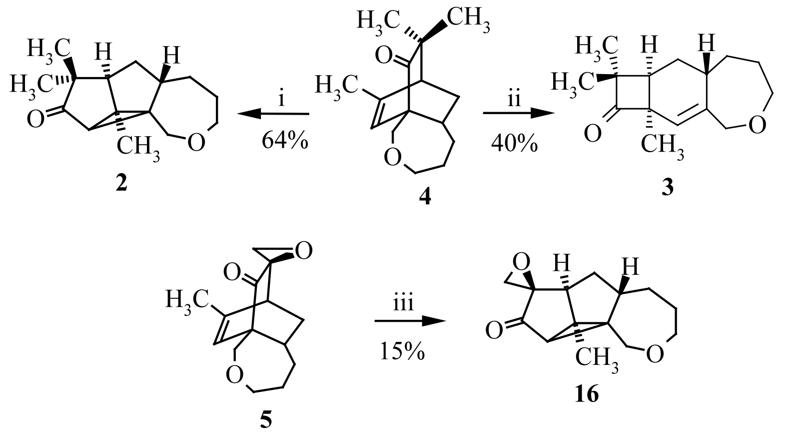


Scheme 3. *Reagents and conditions*: (i) KOH, CTAB, $CHCl_3$–H_2O; (ii) Zn, NH_4Cl, dioxane, Δ; (iii) NaH, THF, CH_3I, Δ; (iv) (a) Jones reagent, acetone, 0–5°C, (b) aq. THF, Δ, 12 h.



Scheme 4. *Reagents and conditions*: (i) *hν*, acetone, 1 h; (ii) *hν*, benzene, 20 min; (iii) *hν*, acetone, acetophenone, 3 h.

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10. Crystal data for **12**: $C_{14}H_{19}ClO_3$, $M=270.74$, orthorhombic, *Pbca*, $Z=8$, $\lambda=0.71073$ Å, $a=13.529(5)$, $b=8.593(2)$, $c=22.595(5)$ Å, $U=2626.8(13)$ Å^3, $T=293(2)$ K, $D_{\text{calcd}}=1.369$ mg/m^3, $\mu=0.289$ mm^{-1}, $F(000)=1152$, size = 0.53×0.43×0.23 mm, reflections collected/unique = 2053/2052 [$R_{\text{int}}=0.0158$], final R indices [$I>2\sigma(I)$]: $R_1=0.0411$, $wR_2=0.0997$, R indices (all data): $R_1=0.0501$, $wR_2=0.1057$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 180965. Copies may be requested free of charge from the director CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: internet +44-1223/336-033; e-mail:deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/conts/retrieving.html].
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